PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16958/WO/03	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/00986	International filing date *(day/month/year)* 21.11.2003	Priority date *(day/month/year)* 22.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/385		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.06.2004	10.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Büttner, U Telephone No. +49 89 2399-7841

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/00986

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-143	as originally filed

Claims, Numbers

7-19, 33-49, 50 (part)	as originally filed
1-6, 20-32, 50 (part)	filed with telefax on 14.02.2005

Drawings, Sheets

1/20-20/20	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 23-28 with respect to Industrial Applicability

   because:

   ☒ the said international application, or the said claims Nos. 23-28 with respect to Industrial Applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. (Claims 1-13, 22-36, 45-50 (all in part); 14, 15, 37, 38) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,34
	No:	Claims	1-6, 8-15,22-33, 35-38, 45-50
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15,22-38,45-50
Industrial applicability (IA)	Yes:	Claims	1-22,29-50
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 14.02.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.
The amendments concerned are the following:
The applicant did not provide any basis for the introduction of the disclaimer " the ROS component is not identical to said beta-blocker component", nor is the IPEA able to identify any basis.
The same applies for the proviso as defined in claim 20 "that at least one of A and E comprises a ROS scavenger group".
A disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation; an anticipation is accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention.
The cited prior art however relates to the same matter and is therefore highly relevant. Therefore the cited prior art cannot be regarded as being accidental.
Preliminary examination is carried out on claims as originally filed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The subject-matter of the present application is not unitary in the sense of rule 13.1 PCT for the following reasons : the problem posed in

the present application was :

Treatment of conditions where a beta-antagonist is indicated such as defined in claim 11.
7 different solutions were identified in the present application :

1.) Use of compounds comprising a beta blocker component derived from a commercially available beta blocker as defined in claim 14, a ROS scavenger component and a NO donor component for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (Claims 1-13, 22-36, 45-50 (all in part); 14, 15, 37, 38)

2.) Use of compounds according to formula I as defined in claim 16, formula IIIA and IVA as defined in claim 18 and compounds 14, 15, 20, 21, 26-35 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (Claims 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part); 16, 39)

3.) Use of compounds according to formula II as defined in claim 17 and compounds 22-25 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (1-13, 19-36, 41, 42, 44-50 (all in part); 17, 40)

4.) Use of compounds according to formula IA as defined in claim 18 (compounds as defined in claims 14 or 15 being excluded) and compounds 1,2,7-24 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (Claims 1-13, 18-36,41-50 (all in part))

5.) Use of compounds according to formula IIA as defined in claim 18 (not being included within formula I and II) and compounds 37, 42, 47, 52, 67, 72, as defined in claim 20 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (Claims 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part))

6.) Use of compounds according to formula VA as defined in claim 18 (not being included within formula I and II) and compounds 39, 40, 44, 45, 49, 50, 54, 55, 69, 70, 74, 75 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (Claims 1-13, 18, 19, 21-36, 41, 42, 44-50 (all in part))

7.) Use of compounds 36, 41, 46, 51, 66, 71 and 38, 43, 48, 53, 68, 73 as defined in claim 21 for the treatment of conditions where a beta antagonist is indicated such as defined in claim 11. (1-13, 20-36, 43-50 (all in part))

Claim 1 suggests the use of compounds comprising a beta blocker component and ROS scavenger component.

Documents D5-D9 disclose that the examined beta-blockers show an antioxidant effect.

Therefore compounds comprising a beta blocker component and ROS scavenger component and their use in the defined conditions are not new.

Claim 2 suggests the use of compounds comprising a beta blocker component and ROS scavenger component and a NO donor component.

Documents D1-D3 and D6 disclose nitrosated beta blockers, for which an antioxidant activity is known (see e.g. D4, D5, D7-D9)) or which at least comprise an antioxidant component as defined in the present application (p. 11, last paragraph).

Therefore compounds comprising a beta blocker component, ROS scavenger component, a NO donor component and their use in the defined conditions are not new.

Therefore the functional features of claims 1 and 2 cannot account any

longer as common inventive concept linking the various items 1-7 above.

Moreover the compounds disclosed in the above mentioned prior art fall within formula III of claim 20 (e.g. timolol, propranolol or also pindolol, carvediol). Therefore formula III is not novel and cannot account any longer as common inventive concept linking the various compounds defined in claim 21.

No common novel inventive structure of different items above could be identified.

Moreover, the IPEA is unable to identify any NOVEL common inventive concept linking the various subject-matters 1 to 7.

Examination has been limited to the first solution (Claims 1-13, 22-36, 45-50 (all in part); 14, 15, 37, 38) .

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: WO 01/35961 A (UNIV BOSTON ;VITA JOSEPH A (US); WORCEL MANUEL (US); LOSCALZO JOSE) 25 May 2001 (2001-05-25)

D2: WO 98/21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22)

D3: WO 00/61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19)

D4: US-A-6 121 328 (WEGLICKI WILLIAM B) 19 September 2000 (2000-09-19)

D5: WO 02/092078 A (TYEBJI ZIAUDDIN Z ;CHARY BALA RAMESHA R (IN); SHANGHVI DILIP SHANT) 21 November 2002 (2002-11-21)

D6: MIZUNO K ET AL: 'Neuroprotective effect and intraocular penetration of nipradilol, a beta-blocker with nitric oxide donative action' INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, ASSOCIATION FOR RESEARCH IN VISION AND, US, vol. 42, no. 3, March 2001 (2001-03), pages 688-694, XP002956392 ISSN: 0146-0404

D7: MARTON Z ET AL: 'Scavenger effect of experimental and clinically used cardiovascular drugs' JOURNAL OF CARDIOVASCULAR PHARMACOLOGY 2001 UNITED STATES, vol. 38, no. 5, 2001, pages 745-753, XP009029273 ISSN: 0160-2446

D8: MOUSA S A ET AL: 'MYOCARDIAL ANTI-ISCHEMIC CHARACTERISTICS OF A NOVEL CLASS OF BETA-ADRENOCEPTOR BLOCKERS' INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY THERAPY AND TOXICOLOGY, vol. 30, no. 3, 1992, pages 103-106, XP009029272 ISSN: 0174-4879

D9: REDDY DOODIPALA SAMBA ET AL: 'Comparative antioxidant effects of beta-adrenoceptor blockers, calcium antagonists and U-74500A against iron-dependent lipid peroxidation in murine ventricular microsomal membranes' METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, vol. 18, no. 9, 1996, pages 559-567, XP009029270 ISSN: 0379-0355

D10: WO 99/37616 A (AENGGAARD ERIK EMIL ;HAJ YEHIA ABDULLAH IBRAHIM (IL)) 29 July 1999 (1999-07-29)

2.) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6, 8-15,22-33, 35-38, 45-50 (and 18-20, 41-43,) is not new in the sense of Article 33(2) PCT.

Document D1 discloses nitrosated beta blockers such as timolol (incorporated by reference of WO9821193) for treating cardiovascular diseases, such as hypertension.
Therefore the subject matter of claims 1-6, 8-15,18-20, 22-33, 35-38, 41-43, 45-50 is not new.

Document D2 discloses that nitrosated timolol shows an improved antihypersensitive activity. Therefore the subject matter of claims 1-6, 8-15,18-20, 22-33, 35-38, 41-43, 45-50 is not new.

Document D3 discloses beta-blockers having a ONO2 group acting as nitric oxide donor for the treatment of myocardial ischaemia or hypertension. Therefore the subject matter of claims 1-6, 8-15,18-20, 22-33, 35-38, 41-43, 45-50 is not new.

Document D6 discloses that nipradilol a beta blocker with nitric oxide donative action protects cells against damage. Therefore the subject matter of claims 1-6, 8-15,18-20, 22-33, 35-38, 41-43, 45-50 is not new.

Document D4 discloses a mixture of D and L-propanol both having an antioxidant activity for the treatment of hypertension, angina, and arrhythmias. Therefore the subject matter of claims 1,3,4,9-14, 20, 22-25, 27-32, 37, 38, 43,45-50 is not new

Document D5 discloses that carvediol has an antioxidant action. Therefore the subject matter of claims 1,3,4,9-14,20,22-25,27-32,37, 43,45-50 is not new.

Documents D7-D9 show that various beta blockers have antioxidant properties. Therefore the subject matter of claims 1,3,4,9-14,20,22-25,27-32,37, 43,45-50 is not new.

3.) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 7 and 34 does not involve an inventive step in the sense of Article 33(3) PCT.

Document D10 discloses the use of piperidine and pyrrolidine derivatives as nitric oxide donors. Therefore the subject matter of claims 7, 34 does not involve an inventive step.

4.) For the assessment of the present claims 23-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03088961	30.10.2003	15.04.2003	19.04.2002

WO03088961 discloses Beta-agonist compounds comprising NO-donors and ROS scavenger groups. It is therefore relevant for the subject matter of claims 1-15, 22-38, 45-50.